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(21) International Application Number: PCT/CN98/00199 (22) International Filing Date: 22 September 1998 (22.09.98) (71) Applicant (for all designated States except US): SHANGHAI SECOND MEDICAL UNIVERSITY [CN/CN]; 197 Ruijin Road II, Shanghai 200025 (CN). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Jialun [CN/CN]; Building 9, Room 1501, 1 Jiande Road, Shanghai 200025 (CN). FU, Gang [CN/CN]; Room 104, 43 Long Shan Xin Cun, Shanghai 200030 (CN). SONG, Huaidong [CN/CN]; Jia Bin Building, Room 405, 227 Chong Qing Road (S), Shanghai 200025 (CN). (74) Agent: CHINA PATENT AGENT (H.K.) LTD.; 22/F, Great Eagle Centre, 23 Harbour Road, Wanchai, Hong Kong Special Administrative Region (CN).		(81) Designated States: CN, US. Published <i>With international search report.</i>
(54) Title: A HUMAN Hsg III GENE (57) Abstract NPCABC08 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing NPCABC08 polypeptides and polynucleotides in therapy, and diagnostic assays for such.		

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A Human Hsg III Gene

Field of the Invention

5 This invention relates to newly identified polypeptides and polynucleotides encoding such polypeptides, to their use in therapy and in identifying compounds which may be agonists, antagonists and/or inhibitors which are potentially useful in therapy, and to production of such polypeptides and polynucleotides.

Background of the Invention

10 The drug discovery process is currently undergoing a fundamental revolution as it embraces 'functional genomics', that is, high throughput genome- or gene-based biology. This approach is rapidly superseding earlier approaches based on 'positional cloning'. A phenotype, that is a biological function or genetic disease, would be identified and this would then be tracked back to the responsible gene, based on its genetic map position.

15 Functional genomics relies heavily on the various tools of bioinformatics to identify gene sequences of potential interest from the many molecular biology databases now available. There is a continuing need to identify and characterise further genes and their related polypeptides/proteins, as targets for drug discovery.

20 Summary of the Invention

The present invention relates to NPCABC08, in particular NPCABC08 polypeptides and NPCABC08 polynucleotides, recombinant materials and methods for their production. In another aspect, the invention relates to methods for using such polypeptides and polynucleotides, including the treatment of cancer, leukemia, diabetes mellitus, kidney disease, autoimmune diseases, and other
25 diseases, hereinafter referred to as "the Diseases", amongst others. In a further aspect, the invention relates to methods for identifying agonists and antagonists/inhibitors using the materials provided by the invention, and treating conditions associated with NPCABC08 imbalance with the identified compounds. In a still further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate NPCABC08 activity or levels.

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Description of the Invention

In a first aspect, the present invention relates to NPCABC08 polypeptides. Such peptides include isolated polypeptides comprising an amino acid sequence which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at

least 95% identity, most preferably at least 97-99% identity; to that of SEQ ID NO:2 over the entire length of SEQ ID NO:2. Such polypeptides include those comprising the amino acid of SEQ ID NO:2.

5 Further peptides of the present invention include isolated polypeptides in which the amino acid sequence has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, most preferably at least 97-99% identity, to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2. Such polypeptides include the polypeptide of SEQ ID NO:2.

10 Further peptides of the present invention include isolated polypeptides encoded by a polynucleotide comprising the sequence contained in SEQ ID NO:1.

Polypeptides of the present invention are believed to be members of the secretogranin III (SgIII) family of polypeptides. They are therefore of interest because the human Hsg III gene is cloned from normal pituitary using EST sequencing. This gene has high similarity with partners in other organisms, may play an important role in signal transduction, and participates in
15 secretory pathways. These properties are hereinafter referred to as "NPCABC08 activity" or "NPCABC08 polypeptide activity" or "biological activity of NPCABC08". Also included amongst these activities are antigenic and immunogenic activities of said NPCABC08 polypeptides, in particular the antigenic and immunogenic activities of the polypeptide of SEQ ID NO:2. Preferably, a polypeptide of the present invention exhibits at least one biological activity
20 of NPCABC08.

The polypeptides of the present invention may be in the form of the "mature" protein or may be a part of a larger protein such as a fusion protein. It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification such as multiple histidine residues, or an additional sequence
25 for stability during recombinant production.

The present invention also includes include variants of the aforementioned polypeptides, that is polypeptides that vary from the referents by conservative amino acid substitutions, whereby a residue is substituted by another with like characteristics. Typical such substitutions are among Ala, Val, Leu and Ile; among Ser and Thr; among the acidic residues Asp and Glu; among Asn and Gln;
30 and among the basic residues Lys and Arg; or aromatic residues Phe and Tyr. Particularly preferred are variants in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids are substituted, deleted, or added in any combination.

Polypeptides of the present invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced

polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to NPCABC08 polynucleotides. Such polynucleotides include isolated polynucleotides comprising a nucleotide sequence encoding a polypeptide which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, to the amino acid sequence of SEQ ID NO:2, over the entire length of SEQ ID NO:2. In this regard, polypeptides which have at least 97% identity are highly preferred, whilst those with at least 98-99% identity are more highly preferred, and those with at least 99% identity are most highly preferred. Such polynucleotides include a polynucleotide comprising the nucleotide sequence contained in SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2.

Further polynucleotides of the present invention include isolated polynucleotides comprising a nucleotide sequence that has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, to a nucleotide sequence encoding a polypeptide of SEQ ID NO:2, over the entire coding region. In this regard, polynucleotides which have at least 97% identity are highly preferred, whilst those with at least 98-99% identity are more highly preferred, and those with at least 99% identity are most highly preferred.

Further polynucleotides of the present invention include isolated polynucleotides comprising a nucleotide sequence which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, to SEQ ID NO:1 over the entire length of SEQ ID NO:1. In this regard, polynucleotides which have at least 97% identity are highly preferred, whilst those with at least 98-99% identity are more highly preferred, and those with at least 99% identity are most highly preferred. Such polynucleotides include a polynucleotide comprising the polynucleotide of SEQ ID NO:1 as well as the polynucleotide of SEQ ID NO:1.

The invention also provides polynucleotides which are complementary to all the above described polynucleotides.

The nucleotide sequence of SEQ ID NO:1 shows homology with mouse secretogranin III (SgIII) mRNA, (A. Dopazo, J. Mol. Neurosci. 1993; 4: 225-233). The nucleotide sequence of SEQ ID NO:1 is a cDNA sequence and comprises a polypeptide encoding sequence (nucleotide 286 to 1689) encoding a polypeptide of 468 amino acids, the polypeptide of SEQ ID NO:2. The nucleotide sequence encoding the polypeptide of SEQ ID NO:2 may be identical to the polypeptide encoding sequence contained in SEQ ID NO:1 or it may be a sequence other than the

one contained in SEQ ID NO:1, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes the polypeptide of SEQ ID NO:2. The polypeptide of SEQ ID NO:2 is structurally related to other proteins of the secretogranin III (SgIII) family, having homology and/or structural similarity with mouse secretogranin III (SgIII) mRNA, (A. Dopazo, J. Mol. Neurosci. 5 1993; 4: 225-233).

Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, preferred polypeptides and polynucleotides of the present invention have at least one NPCABC08 activity.

10 Polynucleotides of the present invention may be obtained, using standard cloning and screening techniques, from a cDNA library derived from mRNA in cells of normal human pituitary, using the expressed sequence tag (EST) analysis (Adams, M.D., *et al. Science* (1991) 252:1651-1656; Adams, M.D. *et al.*, *Nature*, (1992) 355:632-634; Adams, M.D., *et al.*, *Nature* (1995) 377 Supp:3-174). Polynucleotides of the invention can also be obtained from natural sources such as 15 genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the coding sequence for the mature polypeptide, by itself; or the coding sequence for the mature polypeptide in reading 20 frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence which facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, *Proc Natl Acad Sci USA* 25 (1989) 86:821-824, or is an HA tag. The polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Further embodiments of the present invention include polynucleotides encoding polypeptide variants which comprise the amino acid sequence of SEQ ID NO:2 and in which several, for 30 instance from 5 to 10, 1 to 5, 1 to 3, 1 to 2 or 1, amino acid residues are substituted, deleted or added, in any combination.

Polynucleotides which are identical or sufficiently identical to a nucleotide sequence contained in SEQ ID NO:1, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification (PCR) reaction, to isolate full-length cDNAs and genomic

clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes (including genes encoding homologs and orthologs from species other than human) that have a high sequence similarity to SEQ ID NO:1. Typically these nucleotide sequences are 70% identical, preferably 80% identical, more preferably 90% identical, most preferably 95% identical to that of the referent. The probes or primers will generally comprise at least 15 nucleotides, preferably, at least 30 nucleotides and may have at least 50 nucleotides. Particularly preferred probes will have between 30 and 50 nucleotides.

A polynucleotide encoding a polypeptide of the present invention, including homologs and orthologs from species other than human, may be obtained by a process which comprises the steps of screening an appropriate library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO: 1 or a fragment thereof; and isolating full-length cDNA and genomic clones containing said polynucleotide sequence. Such hybridization techniques are well known to the skilled artisan. Preferred stringent hybridization conditions include overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1x SSC at about 65°C. Thus the present invention also includes polynucleotides obtainable by screening an appropriate library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof.

The skilled artisan will appreciate that, in many cases, an isolated cDNA sequence will be incomplete, in that the region coding for the polypeptide is cut short at the 5' end of the cDNA. This is a consequence of reverse transcriptase, an enzyme with inherently low 'processivity' (a measure of the ability of the enzyme to remain attached to the template during the polymerisation reaction), failing to complete a DNA copy of the mRNA template during 1st strand cDNA synthesis.

There are several methods available and well known to those skilled in the art to obtain full-length cDNAs, or extend short cDNAs, for example those based on the method of Rapid Amplification of cDNA ends (RACE) (see, for example, Frohman et al., PNAS USA 85, 8998-9002, 1988). Recent modifications of the technique, exemplified by the Marathon™ technology (Clontech Laboratories Inc.) for example, have significantly simplified the search for longer cDNAs. In the Marathon™ technology, cDNAs have been prepared from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated onto each end. Nucleic acid amplification (PCR) is then carried out to amplify the 'missing' 5' end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is then repeated using

'nested' primers, that is, primers designed to anneal within the amplified product (typically an adaptor specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence). The products of this reaction can then be analyzed by DNA sequencing and a full-length cDNA constructed either by joining the product
5 directly to the existing cDNA to give a complete sequence, or carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

Recombinant polypeptides of the present invention may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems which comprise
10 a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate
15 expression systems or portions thereof for polynucleotides of the present invention. Introduction of polynucleotides into host cells can be effected by methods described in many standard laboratory manuals, such as Davis et al, Basic Methods in Molecular Biology (1986) and Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). Preferred such methods include, for instance, calcium phosphate
20 transfection, DEAE-dextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

Representative examples of appropriate hosts include bacterial cells, such as *streptococci*, *staphylococci*, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and
25 *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

A great variety of expression systems can be used, for instance, chromosomal, episomal and virus-derived systems, e.g., vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from
30 viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector which is able to maintain, propagate or express a

polynucleotide to produce a polypeptide in a host may be used. The appropriate nucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, *MOLECULAR CLONING, A LABORATORY MANUAL* (*supra*). Appropriate secretion signals may be incorporated into the
5 desired polypeptide to allow secretion of the translated protein into the lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the
10 cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid
15 extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during isolation and or purification.

20 This invention also relates to the use of polynucleotides of the present invention as diagnostic reagents. Detection of a mutated form of the gene characterized by the polynucleotide of SEQ ID NO:1 which is associated with a dysfunction will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered expression of the gene. Individuals carrying mutations in the
25 gene may be detected at the DNA level by a variety of techniques.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be
30 detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeledNPCABC08 nucleotide sequences. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in electrophoretic mobility of DNA fragments in gels, with or without

denaturing agents, or by direct DNA sequencing (e.g., Myers *et al.*, *Science* (1985) 230:1242).

Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, *Proc Natl Acad Sci USA* (1985) 85: 4397-4401). In another embodiment, an array of oligonucleotides probes

- 5 comprising NPCABC08 nucleotide sequence or fragments thereof can be constructed to conduct efficient screening of e.g., genetic mutations. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability (see for example: M. Chee *et al.*, *Science*, Vol 274, pp 610-613 (1996)).

- 10 The diagnostic assays offer a process for diagnosing or determining a susceptibility to the Diseases through detection of mutation in the NPCABC08 gene by the methods described. In addition, such diseases may be diagnosed by methods comprising determining from a sample derived from a subject an abnormally decreased or increased level of polypeptide or mRNA. Decreased or increased expression can be measured at the RNA level using any of the methods
- 15 well known in the art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays,
- 20 Western Blot analysis and ELISA assays.

Thus in another aspect, the present invention relates to a diagnostic kit which comprises:

- (a) a polynucleotide of the present invention, preferably the nucleotide sequence of SEQ ID NO: 1, or a fragment thereof;
- (b) a nucleotide sequence complementary to that of (a);
- 25 (c) a polypeptide of the present invention, preferably the polypeptide of SEQ ID NO:2 or a fragment thereof; or
- (d) an antibody to a polypeptide of the present invention, preferably to the polypeptide of SEQ ID NO:2.

- It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial
- 30 component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly cancer, leukemia, diabetes mellitus, kidney disease, and autoimmune diseases, amongst others.

The nucleotide sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to, and can hybridize with, a particular location

on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).

The differences in the cDNA or genomic sequence between affected and unaffected individuals can also be determined. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

The polypeptides of the invention or their fragments or analogs thereof, or cells expressing them, can also be used as immunogens to produce antibodies immunospecific for polypeptides of the present invention. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against polypeptides of the present invention may be obtained by administering the polypeptides or epitope-bearing fragments, analogs or cells to an animal, preferably a non-human animal, using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., *Nature* (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, *Immunology Today* (1983) 4:72) and the EBV-hybridoma technique (Cole *et al.*, *MONOCLONAL ANTIBODIES AND CANCER THERAPY*, pp. 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies, such as those described in U.S. Patent No. 4,946,778, can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography.

Antibodies against polypeptides of the present invention may also be employed to treat the Diseases, amongst others.

In a further aspect, the present invention relates to genetically engineered soluble fusion proteins comprising a polypeptide of the present invention, or a fragment thereof, and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE). Preferred as an immunoglobulin is the constant part of the heavy chain of human IgG, particularly IgG1, where fusion takes place at the hinge region. In a particular embodiment, the Fc part can be removed simply by incorporation of a cleavage sequence which can be cleaved with blood clotting factor Xa. Furthermore, this invention relates to processes for the preparation of these fusion proteins by genetic engineering, and to the use thereof for drug screening, diagnosis and therapy. A further aspect of the invention also relates to polynucleotides encoding such fusion proteins. Examples of fusion protein technology can be found in International Patent Application Nos. WO94/29458 and WO94/22914.

Another aspect of the invention relates to a method for inducing an immunological response in a mammal which comprises inoculating the mammal with a polypeptide of the present invention, adequate to produce antibody and/or T cell immune response to protect said animal from the Diseases hereinbefore mentioned, amongst others. Yet another aspect of the invention relates to a method of inducing immunological response in a mammal which comprises, delivering a polypeptide of the present invention *via* a vector directing expression of the polynucleotide and coding for the polypeptide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases.

A further aspect of the invention relates to an immunological/vaccine formulation (composition) which, when introduced into a mammalian host, induces an immunological response in that mammal to a polypeptide of the present invention wherein the composition comprises a polypeptide or polynucleotide of the present invention. The vaccine formulation may further comprise a suitable carrier. Since a polypeptide may be broken down in the stomach, it is preferably administered parenterally (for instance, subcutaneous, intramuscular, intravenous, or intradermal injection). Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water

systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

Polypeptides of the present invention are responsible for many biological functions, including many disease states, in particular the Diseases hereinbefore mentioned. It is therefore
5 desirous to devise screening methods to identify compounds which stimulate or which inhibit the function of the polypeptide. Accordingly, in a further aspect, the present invention provides for a method of screening compounds to identify those which stimulate or which inhibit the function of the polypeptide. In general, agonists or antagonists may be employed for therapeutic and prophylactic purposes for such Diseases as hereinbefore mentioned. Compounds may be identified
10 from a variety of sources, for example, cells, cell-free preparations, chemical libraries, and natural product mixtures. Such agonists, antagonists or inhibitors so-identified may be natural or modified substrates, ligands, receptors, enzymes, etc., as the case may be, of the polypeptide; or may be structural or functional mimetics thereof (see Coligan *et al.*, *Current Protocols in Immunology* 1(2):Chapter 5 (1991)).

15 The screening method may simply measure the binding of a candidate compound to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve competition with a labeled competitor. Further, these screening methods may test whether the candidate compound results in a signal generated by activation or
20 inhibition of the polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Constitutively active polypeptides may be employed in screening methods for inverse agonists or inhibitors, in the absence of an agonist or inhibitor, by testing whether the candidate
25 compound results in inhibition of activation of the polypeptide. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide of the present invention, to form a mixture, measuring NPCABC08 activity in the mixture, and comparing the NPCABC08 activity of the mixture to a standard. Fusion proteins, such as those made from Fc portion and NPCABC08 polypeptide, as hereinbefore described, can
30 also be used for high-throughput screening assays to identify antagonists for the polypeptide of the present invention (see D. Bennett *et al.*, *J Mol Recognition*, 8:52-58 (1995); and K. Johanson *et al.*, *J Biol Chem*, 270(16):9459-9471 (1995)).

The polynucleotides, polypeptides and antibodies to the polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell associated levels of polypeptide using
5 monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents which may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

The polypeptide may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited
10 to, ligand binding and crosslinking assays in which the polypeptide is labeled with a radioactive isotope (for instance, ^{125}I), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods
15 include biophysical techniques such as surface plasmon resonance and spectroscopy. These screening methods may also be used to identify agonists and antagonists of the polypeptide which compete with the binding of the polypeptide to its receptors, if any. Standard methods for conducting such assays are well understood in the art.

Examples of potential polypeptide antagonists include antibodies or, in some cases, oligonucleotides or proteins which are closely related to the ligands, substrates, receptors, enzymes,
20 etc., as the case may be, of the polypeptide, e.g., a fragment of the ligands, substrates, receptors, enzymes, etc.; or small molecules which bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented.

Thus, in another aspect, the present invention relates to a screening kit for identifying agonists, antagonists, ligands, receptors, substrates, enzymes, etc. for polypeptides of the present
25 invention; or compounds which decrease or enhance the production of such polypeptides, which comprises:

- (a) a polypeptide of the present invention;
 - (b) a recombinant cell expressing a polypeptide of the present invention;
 - (c) a cell membrane expressing a polypeptide of the present invention; or
 - 30 (d) antibody to a polypeptide of the present invention;
- which polypeptide is preferably that of SEQ ID NO:2.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component.

It will be readily appreciated by the skilled artisan that a polypeptide of the present invention may also be used in a method for the structure-based design of an agonist, antagonist or inhibitor of the polypeptide, by:

- (a) determining in the first instance the three-dimensional structure of the polypeptide;
 - 5 (b) deducing the three-dimensional structure for the likely reactive or binding site(s) of an agonist, antagonist or inhibitor;
 - (c) synthesizing candidate compounds that are predicted to bind to or react with the deduced binding or reactive site; and
 - (d) testing whether the candidate compounds are indeed agonists, antagonists or inhibitors.
- 10 It will be further appreciated that this will normally be an interactive process.

In a further aspect, the present invention provides methods of treating abnormal conditions such as, for instance, cancer, leukemia, diabetes mellitus, kidney disease, and autoimmune diseases, related to either an excess of, or an under-expression of, NPCABC08 polypeptide activity.

- If the activity of the polypeptide is in excess, several approaches are available. One
- 15 approach comprises administering to a subject in need thereof an inhibitor compound (antagonist) as hereinabove described, optionally in combination with a pharmaceutically acceptable carrier, in an amount effective to inhibit the function of the polypeptide, such as, for example, by blocking the binding of ligands, substrates, receptors, enzymes, etc., or by inhibiting a second signal, and thereby alleviating the abnormal condition. In another approach, soluble forms of the polypeptides still
- 20 capable of binding the ligand, substrate, enzymes, receptors, etc. in competition with endogenous polypeptide may be administered. Typical examples of such competitors include fragments of the NPCABC08 polypeptide.

- In still another approach, expression of the gene encoding endogenous NPCABC08 polypeptide can be inhibited using expression blocking techniques. Known such techniques
- 25 involve the use of antisense sequences, either internally generated or separately administered (see, for example, O'Connor, *J Neurochem* (1991) 56:560 in *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988)). Alternatively, oligonucleotides which form triple helices with the gene can be supplied (see, for example, Lee *et al.*, *Nucleic Acids Res* (1979) 6:3073; Cooney *et al.*, *Science* (1988) 241:456; Dervan *et al.*,
- 30 *Science* (1991) 251:1360). These oligomers can be administered *per se* or the relevant oligomers can be expressed *in vivo*.

For treating abnormal conditions related to an under-expression of NPCABC08 and its activity, several approaches are also available. One approach comprises administering to a subject a therapeutically effective amount of a compound which activates a polypeptide of the present

invention, i.e., an agonist as described above, in combination with a pharmaceutically acceptable carrier, to thereby alleviate the abnormal condition. Alternatively, gene therapy may be employed to effect the endogenous production of NPCABC08 by the relevant cells in the subject. For example, a polynucleotide of the invention may be engineered for expression in a replication defective
5 retroviral vector, as discussed above. The retroviral expression construct may then be isolated and introduced into a packaging cell transduced with a retroviral plasmid vector containing RNA encoding a polypeptide of the present invention such that the packaging cell now produces infectious viral particles containing the gene of interest. These producer cells may be administered to a subject for engineering cells *in vivo* and expression of the polypeptide *in vivo*. For an overview
10 of gene therapy, see Chapter 20, *Gene Therapy and other Molecular Genetic-based Therapeutic Approaches*, (and references cited therein) in Human Molecular Genetics, T Strachan and A P Read, BIOS Scientific Publishers Ltd (1996). Another approach is to administer a therapeutic amount of a polypeptide of the present invention in combination with a suitable pharmaceutical carrier.

In a further aspect, the present invention provides for pharmaceutical compositions
15 comprising a therapeutically effective amount of a polypeptide, such as the soluble form of a polypeptide of the present invention, agonist/antagonist peptide or small molecule compound, in combination with a pharmaceutically acceptable carrier or excipient. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The invention further relates to pharmaceutical packs and kits comprising one or more containers
20 filled with one or more of the ingredients of the aforementioned compositions of the invention. Polypeptides and other compounds of the present invention may be employed alone or in conjunction with other compounds, such as therapeutic compounds.

The composition will be adapted to the route of administration, for instance by a systemic or an oral route. Preferred forms of systemic administration include injection, typically by intravenous
25 injection. Other injection routes, such as subcutaneous, intramuscular, or intraperitoneal, can be used. Alternative means for systemic administration include transmucosal and transdermal administration using penetrants such as bile salts or fusidic acids or other detergents. In addition, if a polypeptide or other compounds of the present invention can be formulated in an enteric or an encapsulated formulation, oral administration may also be possible. Administration of these
30 compounds may also be topical and/or localized, in the form of salves, pastes, gels, and the like.

The dosage range required depends on the choice of peptide or other compounds of the present invention, the route of administration, the nature of the formulation, the nature of the subject's condition, and the judgment of the attending practitioner. Suitable dosages, however, are in the range of 0.1-100 µg/kg of subject. Wide variations in the needed dosage, however, are to be

expected in view of the variety of compounds available and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art.

5 Polypeptides used in treatment can also be generated endogenously in the subject, in treatment modalities often referred to as "gene therapy" as described above. Thus, for example, cells from a subject may be engineered with a polynucleotide, such as a DNA or RNA, to encode a polypeptide *ex vivo*, and for example, by the use of a retroviral plasmid vector. The cells are then introduced into the subject.

10 Polynucleotide and polypeptide sequences form a valuable information resource with which to identify further sequences of similar homology. This is most easily facilitated by storing the sequence in a computer readable medium and then using the stored data to search a sequence database using well known searching tools, such as GCC. Accordingly, in a further aspect, the present invention provides for a computer readable medium having stored thereon a
15 polynucleotide comprising the sequence of SEQ ID NO:1 and/or a polypeptide sequence encoded thereby.

The following definitions are provided to facilitate understanding of certain terms used frequently hereinbefore.

20 "Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from the natural state. If an "isolated" composition or substance occurs in nature, it has been changed or removed from its original
25 environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living animal is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein.

"Polynucleotide" generally refers to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotides" include,
30 without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both

RNA and DNA. The term "polynucleotide" also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

"Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus, "polynucleotide" embraces

5 chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells.

"Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

10 "Polypeptide" refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification

15 techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present to the same or varying degrees at several sites in a given polypeptide. Also, a given

20 polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a

25 nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing,

30 phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993; Wold, F., Post-translational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in POSTTRANSLATIONAL COVALENT

MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", *Meth Enzymol* (1990) 182:626-646 and Rattan *et al.*, "Protein Synthesis: Post-translational Modifications and Aging", *Ann NY Acad Sci* (1992) 663:48-62).

5 "Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains essential properties. A typical variant of a polynucleotide differs in nucleotide sequence from another, reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino
10 acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from another, reference polypeptide. Generally, differences are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one
15 or more substitutions, additions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. A variant of a polynucleotide or polypeptide may be a naturally occurring such as an allelic variant, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis.

20 "Identity," as known in the art, is a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by known methods,
25 including but not limited to those described in (*Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*,
30 Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., *SIAM J. Applied Math.*, 48: 1073 (1988). Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not

limited to, the GCG program package (Devereux, J., et al., *Nucleic Acids Research* 12(1): 387 (1984)), BLASTP, BLASTN, and FASTA (Atschul, S.F. et al., *J. Molec. Biol.* 215: 403-410 (1990)). The BLAST X program is publicly available from NCBI and other sources (*BLAST Manual*, Altschul, S., et al., NCBI NLM NIH Bethesda, MD 20894; Altschul, S., et al., *J. Mol. Biol.* 215: 403-410 (1990)). The well known Smith Waterman algorithm may also be used to determine identity.

Preferred parameters for polypeptide sequence comparison include the following:

1) Algorithm: Needleman and Wunsch, *J. Mol Biol.* 48: 443-453 (1970)

Comparison matrix: BLOSSUM62 from Hentikoff and Hentikoff, *Proc. Natl. Acad. Sci. USA.* 89:10915-10919 (1992)

Gap Penalty: 12

Gap Length Penalty: 4

A program useful with these parameters is publicly available as the "gap" program from Genetics Computer Group, Madison WI. The aforementioned parameters are the default parameters for peptide comparisons (along with no penalty for end gaps).

Preferred parameters for polynucleotide comparison include the following:

1) Algorithm: Needleman and Wunsch, *J. Mol Biol.* 48: 443-453 (1970)

Comparison matrix: matches = +10, mismatch = 0

Gap Penalty: 50

Gap Length Penalty: 3

Available as: The "gap" program from Genetics Computer Group, Madison WI. These are the default parameters for nucleic acid comparisons.

By way of example, a polynucleotide sequence of the present invention may be identical to the reference sequence of SEQ ID NO:1, that is be 100% identical, or it may include up to a certain integer number of nucleotide alterations as compared to the reference sequence. Such alterations are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion, and wherein said alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleotide alterations is determined by multiplying the total number of nucleotides in SEQ ID NO:1 by the numerical percent of the respective percent identity (divided by 100) and subtracting that product from said total number of nucleotides in SEQ ID NO:1, or:

$$n_n \leq x_n - (x_n \cdot y),$$

wherein n_n is the number of nucleotide alterations, x_n is the total number of nucleotides in SEQ ID NO:1, and y is, for instance, 0.70 for 70%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, etc., and wherein any non-integer product of x_n and y is rounded down to the nearest integer prior to subtracting it from x_n . Alterations of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:2 may create nonsense, missense or frameshift mutations in this coding sequence and thereby alter the polypeptide encoded by the polynucleotide following such alterations.

Similarly, a polypeptide sequence of the present invention may be identical to the reference sequence of SEQ ID NO:2, that is be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the % identity is less than 100%. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in SEQ ID NO:2 by the numerical percent of the respective percent identity (divided by 100) and then subtracting that product from said total number of amino acids in SEQ ID NO:2, or:

$$n_a \leq x_a - (x_a \cdot y),$$

wherein n_a is the number of amino acid alterations, x_a is the total number of amino acids in SEQ ID NO:2, and y is, for instance 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc., and wherein any non-integer product of x_a and y is rounded down to the nearest integer prior to subtracting it from x_a .

"Fusion protein" refers to a protein encoded by two, often unrelated, fused genes or fragments thereof. In one example, EP-A-0 464 discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, employing an immunoglobulin Fc region as a part of a fusion protein is advantageous for use in therapy and diagnosis resulting in, for example, improved pharmacokinetic properties [see, e.g., EP-A 0232 262]. On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

5

SEQUENCE INFORMATION

SEQ ID NO:1

TAAAGCTACGCCCTGGCCGCGAGTCTCCGCGTCACAGGAACTTCAGCACCCACAGGGCGGA
CAGCGCTCCCCCTCTACCTGGAGACTTGACTCCCGCGCGCCCCAACCTGCTTATCCCTTG
5 ACCGTCGAGTGTCTAGAGATCCTGCAGCCGCCAGTCCCGGCCCCCTCTCCCGCCCCACACC
CACCCCTCCTGGCTCTTCCTGTTTTTACTCCTCCTTTTCATTCATAACAAAAGCTACAGCT
CCAGGAGCCCAGCGCCGGGCTGTGACCCAAGCCGAGCGTGGAAGAATGGGGTTCCTCGGG
ACCGGCACTTGGATTCTGGTGTTAGTGCTCCCGATTCAAGCTTTCCCCAAACCTGGAGGA
AGCCAAGACAAATCTCTACATAATAGAGAATTAAGTGCAGAAAGACCTTTGAATGAACAG
10 ATTGCTGAAGCAGAAGAAGACAAGATTAAAAAACATATCCTCCAGAAAACAAGCCAGGT
CAGAGCAACTATTCTTTTGTGATAACTTGAACCTGCTAAGGGCAATAACAGAAAAGGAA
AAAATTGAGAAAGAAAGACAATCTATAAGAAGCTCCCCACTTGATAATAAGTTGAATGTG
GAAGATGTTGATTCAACCAAGAATCGAAAAGTATCGATGATTATGACTCTACTAAGAGT
GGATTGGATCATAAATTTCAAGATGATCCAGATGGTCTTCATCAACTAGACGGGACTCCT
15 TTAACCGCTGAAGACATTGTCCATAAAATCGCTGCCAGGATTTATGAAGAAAATGACAGA
GCCGTGTTTGACAAGATTGTTTCTAACTACTTAATCTCGGCCTTATCACAGAAAGCCAA
GCACATACACTGGAAGATGAAGTAGCAGAGGTTTTACAAAAATTAATCTCAAAGGAAGCC
AACAATTATGAGGAGGATCCCAATAAGCCCACAAGCTGGACTGAGAATCAGGCTGGAAAA
ATACCAGAGAAAGTGACTCCAATGGCAGCAATTCAAGATGGTCTTGCTAAGGGAGAAAAAC
20 GATGAAACAGTATCTAACACATTAACCTTGACAAATGGCTTGAAAGGAGAACTAAACC
TACAGTGAAGACAACCTTTAGGGACTTCCAATATTTCCCAAATTTCTATGCGCTACTGAAA
AGTATTGATTCAGAAAAAGAAGCAAAAGAGAAAGAAACACTGATTACTATCATGAAAACA
CTGATTGACTTTGTGAAGATGATGGTGAAATATGGAACAATATCTCCAGAAGAAGGTGTT
TCCTACCTTGAAAACCTTGATGAAATGATTGCTCTTCAGACCAAAAACAAGCTAGAAAAA
25 AATGCTACTGACAATATAAGCAAGCTTTTCCCAGCACCATCAGAGAAGAGTCATGAAGAA
ACAGACAGTACCAAGGAAGAAGCAGCTAAGATGGAAAAGGAATATGGAAGCTTGAAGGAT
TCCACAAAAGATGATAACTCCAACCCAGGAGGAAAGACAGATGAACCCAAAGGAAAAACA
GAAGCCTATTTGGAAGCCATCAGAAAAAATATTGAATGGTTGAAGAAACATGACAAAAAG
GGAAATAAAGAAGATTATGACCTTTCAAAGATGAGAGACTTCATCAATAAACAAGCTGAT
30 GCTTATGTGGAGAAAGGCATCCTTGACAAGGAAGAAGCCGAGGCCATCAAGCGCATTAT
AGCAGCCTGTAAAAATGGCAAAAGATCCAGGAGTCTTCAACTGTTTCAGAAAACATAAT
ATAGCTTAAACACTTCTAATTCTGTGATTAAATTTTTTGACCCAAGGGTTATTAGAAA
GTGCTGAATTTACAGTAGTTAACCTTTTACAAGTGTTTAAACATAGCTTTCTTCCCGTA
AAAATATCTGAAAGTAAAGTTGTATGTAAGCTGAGATTTTGTATACAGGAATCCTTATT
35 TCCTCATAGNCTTATTATTTTATAATCAGGAATATGTTGCTTTGGAAAAAGCCTCTTAAT
GGGCTGACCNTAAAACTCAATCCNTCTTCCACTGTC

SEQ ID NO:2

MGFLGTGTWILVVLPIQAFPKPGGSQDKSLHNRELSAERPLNEQIAEAEEDKIKKTYPP
ENKPGQSNYSFVDNLNLLRAITEKEKIEKERQSIRSSPLDNKLNVEDVDSTKNRKLIDDY
DSTKSGLDHKFQDDPDGLHQLDGTPLTAEDIVHKIAARIYEENDRAVFDKIVSKLLNLGL
5 ITESQAHTLEDEVAEVLQKLISKEANNYEEDPNKPTSWTENQAGKIKEKVTPMAAIQDGL
AKGENDETVSNTLTLTNGLERRTKTYSEDNFRDFQYFPNIFYALLKSIDSEKEAKEKETLI
TIMKTLIDFVKMMVKYGTISPEEGVSYLENLDEMIALQTKNKLEKNATDNISKLFAPSE
KSHEETDSTKEEAAKMEKEYGSLKDSTKDDNSNPGGKTDEPKGKTEAYLEAIRKNIEWLK
KHDKKGNKEDYDLSKMRDFINKQADAYVEKGILDKEEAEAIKRIYSSL

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:
- 5 (i) an isolated polypeptide comprising an amino acid sequence selected from the group having at least:
- (a) 70% identity;
- (b) 80% identity;
- (c) 90% identity; or
- (d) 95% identity
- 10 to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2;
- (ii) an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 or
- (iii) an isolated polypeptide which is the amino acid sequence of SEQ ID NO:2.
- 15 2. An isolated polynucleotide selected from the group consisting of:
- (i) an isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide that has at least
- (a) 70% identity;
- (b) 80% identity;
- 20 (c) 90% identity; or
- (d) 95% identity;
- to the amino acid sequence of SEQ ID NO:2, over the entire length of SEQ ID NO:2;
- (ii) an isolated polynucleotide comprising a nucleotide sequence that has at least:
- (a) 70% identity
- 25 (b) 80% identity;
- (c) 90% identity; or
- (d) 95% identity;
- over its entire length to a nucleotide sequence encoding the polypeptide of SEQ ID NO:2;
- 30 (iii) an isolated polynucleotide comprising a nucleotide sequence which has at least:
- (a) 70% identity;
- (b) 80% identity;
- (c) 90% identity; or
- (d) 95% identity;

to that of SEQ ID NO: 1 over the entire length of SEQ ID NO:1;

(iv) an isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2;

(vi) an isolated polynucleotide which is the polynucleotide of SEQ ID NO: 1; or

5 (vi) an isolated polynucleotide obtainable by screening an appropriate library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO: 1 or a fragment thereof;

or a nucleotide sequence complementary to said isolated polynucleotide.

10 3. An antibody immunospecific for the polypeptide of claim 1.

4. A method for the treatment of a subject:

(i) in need of enhanced activity or expression of the polypeptide of claim 1 comprising:

15 (a) administering to the subject a therapeutically effective amount of an agonist to said polypeptide; and/or

(b) providing to the subject an isolated polynucleotide comprising a nucleotide sequence encoding said polypeptide in a form so as to effect production of said polypeptide activity *in vivo.*; or

20 (ii) having need to inhibit activity or expression of the polypeptide of claim 1 comprising:

(a) administering to the subject a therapeutically effective amount of an antagonist to said polypeptide; and/or

(b) administering to the subject a nucleic acid molecule that inhibits the expression of a nucleotide sequence encoding said polypeptide; and/or

25 (c) administering to the subject a therapeutically effective amount of a polypeptide that competes with said polypeptide for its ligand, substrate, or receptor.

30 5. A process for diagnosing a disease or a susceptibility to a disease in a subject related to expression or activity of the polypeptide of claim 1 in a subject comprising:

(a) determining the presence or absence of a mutation in the nucleotide sequence encoding said polypeptide in the genome of said subject; and/or

(b) analyzing for the presence or amount of said polypeptide expression in a sample derived from said subject.

6. A method for screening to identify compounds which stimulate or which inhibit the function of the polypeptide of claim 1 which comprises a method selected from the group consisting of:
- 5 (a) measuring the binding of a candidate compound to the polypeptide (or to the cells or membranes bearing the polypeptide) or a fusion protein thereof by means of a label directly or indirectly associated with the candidate compound;
 - (b) measuring the binding of a candidate compound to the polypeptide (or to the cells or membranes bearing the polypeptide) or a fusion protein thereof in the presence of a labeled competitor;
 - 10 (c) testing whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells or cell membranes bearing the polypeptide;
 - (d) mixing a candidate compound with a solution containing a polypeptide of claim 1, to form a mixture, measuring activity of the polypeptide in the mixture, and comparing
 - 15 the activity of the mixture to a standard; or
 - (e) detecting the effect of a candidate compound on the production of mRNA encoding said polypeptide and said polypeptide in cells, using for instance, an ELISA assay.
7. An agonist or an antagonist of the polypeptide of claim 1.
- 20 8. An expression system comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression system is present in a compatible host cell.
9. A process for producing a recombinant host cell comprising transforming or transfecting a cell
- 25 with the expression system of claim 8 such that the host cell, under appropriate culture conditions, produces a polypeptide comprising an amino acid sequence having at least 70% identity to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2.
10. A recombinant host cell produced by the process of claim 9.
- 30 11. A membrane of a recombinant host cell of claim 10 expressing a polypeptide comprising an amino acid sequence having at least 70% identity to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2.

12. A process for producing a polypeptide comprising culturing a host cell of claim 10 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture.

SEQUENCE LISTING

(1) GENERAL INFORMATION

- (i) APPLICANT: SHANGHAI SECOND MEDICAL UNIVERSITY
- (ii) TITLE OF THE INVENTION: A HUMAN HSG III GENE
- (iii) NUMBER OF SEQUENCES: 2
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Ratner & Prestia
 - (B) STREET: P.O. Box 980
 - (C) CITY: Valley Forge
 - (D) STATE: PA
 - (E) COUNTRY: USA
 - (F) ZIP: 19482
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette
 - (B) COMPUTER: IBM Compatible
 - (C) OPERATING SYSTEM: DOS
 - (D) SOFTWARE: FastSEQ for Windows Version 2.0
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: TO BE ASSIGNED
 - (B) FILING DATE:
 - (C) CLASSIFICATION: UNKNOWN
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Prestia, Paul F
 - (B) REGISTRATION NUMBER: 23,031
 - (C) REFERENCE/DOCKET NUMBER: GP-70526
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 610-407-0700
 - (B) TELEFAX: 610-407-0700
 - (C) TELEX: 846169

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2017 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

TAAAGCTACG CCCTGGCCGC AGTCTCCGCG TCACAGGAAC TTCAGCACCC ACAGGGCGGA      60
CAGCGCTCCC CTCTACCTGG AGACTTGACT CCCGCGCGCC CCAACCCCTGC TTATCCCTTG      120
ACCGTCGAGT GTCAGAGATC CTGCAGCCGC CCAGTCCCCGG CCCCTCTCCC GCCCCACACC      180
CACCTCCTTG GCTCTTCCTG TTTTACTCC TCCTTTTCAT TCATAACAAA AGCTACAGCT      240
CCAGGAGCCC AGCGCCGGGC TGTGACCCAA GCCGAGCGTG GAAGAATGGG GTTCCTCGGG      300
ACCGGCACTT GGATTCTGGT GTTAGTGCTC CCGATTCAAG CTTTCCCCAA ACCTGGAGGA      360
AGCCAAGACA AATCTCTACA TAATAGAGAA TTAAGTGCAG AAAGACCTTT GAATGAACAG      420
ATTGCTGAAG CAGAAGAAGA CAAGATTAAA AAAACATATC CTCCAGAAAA CAAGCCAGGT      480
CAGAGCAACT ATTCTTTTGT TGATAACTTG AACCTGCTAA GGGCAATAAC AGAAAAGGAA      540
AAAATTGAGA AAGAAAGACA ATCTATAAGA AGCTCCCCAC TTGATAATAA GTTGAATGTG      600
GAAGATGTTG ATTCAACCAA GAATCGAAAA CTGATCGATG ATTATGACTC TACTAAGAGT      660
GGATTGGATC ATAAATTTCA AGATGATCCA GATGGTCTTC ATCAACTAGA CGGGACTCCT      720
TTAACCGCTG AAGACATTGT CCATAAAATC CCGCCAGGA TTTATGAAGA AAATGACAGA      780
GCCGTGTTTG ACAAGATTGT TTCTAACTA CTTAATCTCG GCCTTATCAC AGAAAGCCAA      840
GCACATACAC TGGAAGATGA AGTAGCAGAG GTTTTACAAA AATTAATCTC AAAGGAAGCC      900
AACAAATTATG AGGAGGATCC CAATAAGCCC ACAAGCTGGA CTGAGAATCA GGCTGGAAAA      960
ATACCAGAGA AAGTGACTCC AATGGCAGCA ATTCAAGATG GTCTTGCTAA GGGAGAAAAC      1020
GATGAAACAG TATCTAACAC ATTAACCTTG ACAAATGGCT TGGAAAGGAG AACTAAAACC      1080
TACAGTGAAG ACAACTTTAG GGACTTCCAA TATTTCCCAA ATTTCTATGC GCTACTGAAA      1140
AGTATTGATT CAGAAAAAGA AGCAAAAGAG AAAGAAACAC TGATTACTAT CATGAAAACA      1200
CTGATTGATT TTGTGAAGAT GATGGTGAAA TATGGAACAA TATCTCCAGA AGAAGGTGTT      1260
TCCTACCTTG AAAAATTGGA TGAAATGATT GCTCTTCAGA CCAAAAACAA GCTAGAAAAA      1320
AATGCTACTG ACAATATAAG CAAGCTTTTC CCAGCACCAT CAGAGAAGAG TCATGAAGAA      1380
ACAGACAGTA CCAAGGAAGA AGCAGCTAAG ATGGAAGAGG AATATGGAAG CTGGAAGGAT      1440
TCCACAAAAG ATGATAACTC CAACCCAGGA GGAAAGACAG ATGAACCCAA AGGAAAAACA      1500
GAAGCCTATT TGGAAGCCAT CAGAAAAAAT ATTGAATGGT TGAAGAAACA TGACAAAAAG      1560
GGAAATAAAG AAGATTATGA CCTTTCAAAG ATGAGAGACT TCATCAATAA ACAAGCTGAT      1620
GCTTATGTGG AGAAAGGCAT CCTTGACAAG GAAGAAGCCG AGGCCATCAA GCGCATTTAT      1680
AGCAGCCTGT AAAAATGGCA AAAGATCCAG GAGTCTTTCA ACTGTTTCAG AAAACATAAT      1740
ATAGCTTAAA ACACTTCTAA TTCTGTGATT AAAATTTTTT GACCCAAGGG TTATTAGAAA      1800
GTGCTGAATT TACAGTAGTT AACCTTTTAC AAGTGGTTAA AACATAGCTT TCTTCCCCTA      1860
AAACTATCTT GAAAGTAAAG TTGTATGTAA GCTGAGATTT TGTATACAGG AATCCTTATT      1920
TCCTCATAGN CTTATTATTT TATAATCAGG AATATGTTGC TTTGGAAAAA GCCTCTTAAT      1980
GGGCTGACCN TAAAAACTCA ATCCNTCTTC CACTGTC      2017

```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 468 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Gly Phe Leu Gly Thr Gly Thr Trp Ile Leu Val Leu Val Leu Pro
 1           5           10           15
Ile Gln Ala Phe Pro Lys Pro Gly Gly Ser Gln Asp Lys Ser Leu His
          20          25          30
Asn Arg Glu Leu Ser Ala Glu Arg Pro Leu Asn Glu Gln Ile Ala Glu
                        2/3

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			35				40				45				
Ala	Glu	Glu	Asp	Lys	Ile	Lys	Lys	Thr	Tyr	Pro	Pro	Glu	Asn	Lys	Pro
	50					55					60				
Gly	Gln	Ser	Asn	Tyr	Ser	Phe	Val	Asp	Asn	Leu	Asn	Leu	Leu	Arg	Ala
65					70				75					80	
Ile	Thr	Glu	Lys	Glu	Lys	Ile	Glu	Lys	Glu	Arg	Gln	Ser	Ile	Arg	Ser
			85						90				95		
Ser	Pro	Leu	Asp	Asn	Lys	Leu	Asn	Val	Glu	Asp	Val	Asp	Ser	Thr	Lys
			100					105					110		
Asn	Arg	Lys	Leu	Ile	Asp	Asp	Tyr	Asp	Ser	Thr	Lys	Ser	Gly	Leu	Asp
		115					120					125			
His	Lys	Phe	Gln	Asp	Asp	Pro	Asp	Gly	Leu	His	Gln	Leu	Asp	Gly	Thr
130						135					140				
Pro	Leu	Thr	Ala	Glu	Asp	Ile	Val	His	Lys	Ile	Ala	Ala	Arg	Ile	Tyr
145					150					155					160
Glu	Glu	Asn	Asp	Arg	Ala	Val	Phe	Asp	Lys	Ile	Val	Ser	Lys	Leu	Leu
			165						170					175	
Asn	Leu	Gly	Leu	Ile	Thr	Glu	Ser	Gln	Ala	His	Thr	Leu	Glu	Asp	Glu
			180					185					190		
Val	Ala	Glu	Val	Leu	Gln	Lys	Leu	Ile	Ser	Lys	Glu	Ala	Asn	Asn	Tyr
		195					200					205			
Glu	Glu	Asp	Pro	Asn	Lys	Pro	Thr	Ser	Trp	Thr	Glu	Asn	Gln	Ala	Gly
210						215					220				
Lys	Ile	Pro	Glu	Lys	Val	Thr	Pro	Met	Ala	Ala	Ile	Gln	Asp	Gly	Leu
225					230					235					240
Ala	Lys	Gly	Glu	Asn	Asp	Glu	Thr	Val	Ser	Asn	Thr	Leu	Thr	Leu	Thr
			245						250					255	
Asn	Gly	Leu	Glu	Arg	Arg	Thr	Lys	Thr	Tyr	Ser	Glu	Asp	Asn	Phe	Arg
			260					265					270		
Asp	Phe	Gln	Tyr	Phe	Pro	Asn	Phe	Tyr	Ala	Leu	Leu	Lys	Ser	Ile	Asp
	275					280						285			
Ser	Glu	Lys	Glu	Ala	Lys	Glu	Lys	Glu	Thr	Leu	Ile	Thr	Ile	Met	Lys
290						295					300				
Thr	Leu	Ile	Asp	Phe	Val	Lys	Met	Met	Val	Lys	Tyr	Gly	Thr	Ile	Ser
305					310					315					320
Pro	Glu	Glu	Gly	Val	Ser	Tyr	Leu	Glu	Asn	Leu	Asp	Glu	Met	Ile	Ala
			325						330					335	
Leu	Gln	Thr	Lys	Asn	Lys	Leu	Glu	Lys	Asn	Ala	Thr	Asp	Asn	Ile	Ser
			340					345					350		
Lys	Leu	Phe	Pro	Ala	Pro	Ser	Glu	Lys	Ser	His	Glu	Glu	Thr	Asp	Ser
		355					360					365			
Thr	Lys	Glu	Glu	Ala	Ala	Lys	Met	Glu	Lys	Glu	Tyr	Gly	Ser	Leu	Lys
370						375					380				
Asp	Ser	Thr	Lys	Asp	Asp	Asn	Ser	Asn	Pro	Gly	Gly	Lys	Thr	Asp	Glu
385					390					395					400
Pro	Lys	Gly	Lys	Thr	Glu	Ala	Tyr	Leu	Glu	Ala	Ile	Arg	Lys	Asn	Ile
			405						410					415	
Glu	Trp	Leu	Lys	Lys	His	Asp	Lys	Lys	Gly	Asn	Lys	Glu	Asp	Tyr	Asp
			420					425					430		
Leu	Ser	Lys	Met	Arg	Asp	Phe	Ile	Asn	Lys	Gln	Ala	Asp	Ala	Tyr	Val
		435					440					445			
Glu	Lys	Gly	Ile	Leu	Asp	Lys	Glu	Glu	Ala	Glu	Ala	Ile	Lys	Arg	Ile
	450					455					460				
Tyr	Ser	Ser	Leu												
465															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN98/00199

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶ C12N15/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched(classification system followed by classification symbols)

IPC⁶ C12N15/12

Documentation searched other than minimum documentation to the extent that such documents are included in the field searched

Electronic data base consulted during the international search(name of data base and, where practicable, search terms used)

EPOQUE (WPI) , CNPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant claim No.
A	JP, A, 6228002(TAKEDA CHEM IND LTD) 16 Autumn 1994, See the whole document	1-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search
20 May 1999 (20. 05. 99)

Date of mailing of the international search report

27 MAY 1999 (27. 05. 99)

Name and mailing address of the ISA/
The Chinese Patent Office
6, Xitucheng Road, Haidian District,
Beijing, 100088, China

Facsimile No. 86-10-62019451

Authorized officer PAN, Aiqun

Telephone No.

(86-10)62093906

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN98/00199

Patent document cited in search report	Publication date	Patent family members	Publication date
JP-A- 6228002	16.08.94	none	

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C12N 15/12	A1	(11) International Publication Number: WO 00/17349 (43) International Publication Date: 30 March 2000 (30.03.00)
<p>(21) International Application Number: PCT/CN98/00199</p> <p>(22) International Filing Date: 22 September 1998 (22.09.98)</p> <p>(71) Applicant (for all designated States except US): SHANGHAI SECOND MEDICAL UNIVERSITY [CN/CN]; 197 Ruijin Road II, Shanghai 200025 (CN).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): CHEN, Jialun [CN/CN]; Building 9, Room 1501, 1 Jiande Road, Shanghai 200025 (CN). FU, Gang [CN/CN]; Room 104, 43 Long Shan Xin Cun, Shanghai 200030 (CN). SONG, Huaidong [CN/CN]; Jia Bin Building, Room 405, 227 Chong Qing Road (S), Shanghai 200025 (CN).</p> <p>(74) Agent: CHINA PATENT AGENT (H.K.) LTD.; 22/F, Great Eagle Centre, 23 Harbour Road, Wanchai, Hong Kong Special Administrative Region (CN).</p>		<p>(81) Designated States: CN, US.</p> <p>Published With international search report.</p>
<p>(54) Title: A HUMAN Hsg III GENE</p> <p>(57) Abstract</p> <p>NPCABC08 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing NPCABC08 polypeptides and polynucleotides in therapy, and diagnostic assays for such.</p>		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN98/00199

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EPOQUE (WPI), CNPAT

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